REMARKS

Claim amendments

Claims 5, 8, 11, and 13-21 are currently pending in the application.

Rejections under 35 U.S.C. § 103

(1) Claims 5, 8, 11 13 and 15-20 stand are rejected under 35 U.S.C. § 103 as being unpatentable over Avidano et al. in view of Lezdey (U.S. Patent No. 6,174,859).

Avidano et al., allegedly teaches that otorrhea samples were collected from human patients with otitis media and a perforated tympanic membrane and the samples were treated with ilomostat plus alpha 1-antitypsin ***in vitro***. Avidano et al., do not teach the actual ***in vivo*** treatment of a human patient with a perforated tympanic membrane with an effective amount of ilomostat plus alpha 1-antitrypsin.

Lezdey et al., allegedly teaches a composition comprising alpha 1-antitrypsin and a steroid compound for patients in vivo suffering from ear infections caused by pseudomonas.

It allegedly would have been obvious to one of ordinary skill to treat patients ***in vivo*** with otitis media with a perforated tympanic membrane with alpha 1-antitrypsin without significant ototoxicity because Avidano obtained a statistically significant decrease in protease activity against *Pseudomonas* from a sample obtained from humans who had otitis media and because the effective therapeutic amount of alpha 1-antitrypsin for the treatment of ear infections caused by *Pseudomonas* is well known by Lezdey et al. One would allegedly be motivated to employ the teaching of Avidano to a patient actually suffering from an ear infection in order to achieve an expected benefit of actual effect *in vivo*. Moreover, to further incorporate an effective amount of steroid in the method is allegedly obvious because Lezdey et al., teaches that steroids are routinely combined with alpha 1-antitrypsin for patients suffering from ear infections caused by *Pseudomonas*. Absent any evidence to the contrary, there would have allegedly been a

reasonable expectation of successfully treating an individual having otitis media and a perforated tympanic membrane with alpha 1-antitrypsin well known by Avidano et al., having significant antiprotease activity in human otitis media samples.

Applicants traverse the rejection for the following reasons.

The claimed invention recites a method of treating an individual having otitis media and a perforated tympanic membrane comprising administering an effective, nonototoxic amound of rAAT to the middle ear by topical application to the external auditory canal wherein the otitis media is treated without significant ototoxicity.

The Applicants respectfully submit that the Examiner has failed to make out a *prima facie* case of obviousness. In order to establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999).

Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531.

Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, the references fail to teach or suggest all of the claim elements. Specifically, none of the references, either alone or when combined, teach or suggest a method that includes delivering to any individual, much less an individual having otitis media and a

perforated tympanic membrane, an effective, nonototoxic amount of recombinant AAT to the middle ear by topical application to the external auditory canal wherein the otitis media is treated without significant ototoxicity.

Avidano discloses ***in vitro*** assays for proteases on samples obtained from patients with otorrhea resulting from tympanic membrane perforations or pressure-equalization tubes. However, Avidano fails to disclose any methods of treatment. The Examiner agrees that Avidano does not teach the actual *in vivo* treatment of an individual having otitis media with a perforated typanic membrane.

Lezdey et al., teaches the administration of alpha 1-antitrypsin, a secretary protease inhibitor, can be delivered in an aqueous or ointment base for ophthalmologic and otolaryngologic application. Lezdey et al., teaches that the alpha 1-antitrypsin can be combined with thickeners, such as hydroxypropyl methyl cellulose, with steroidal antiphlogistics such as indomethacin or antibiotics such as bacitracin, neomycin, tetracycline or chloramphenicol and hyaluronic acid. Lezdey in Example 2 teaches the administration to a patient with swimmer's ear, alpha 1-antitrypsin, hydroxypropyl methyl cellulose and phosphate buffer. Lezdey does not teach or suggest the administration of alpha 1-antitrypsin to patients with a perforated tympanic membrane. Lezdey does not discuss the possible ototoxic effects of delivery of alpha 1-antitrypsin, antibiotics, steroidals or ilomastat into the ear trough a perforated tympanic membrane. Lezdey et al. actually teaches away from the administration of alpha 1-antitrypsin to patients with a perforated tympanic membrane because Lezdey teaches combining the alpha 1-antitrypsin with antibiotics which are known to be ototoxic.

A combination of the references does not teach the claimed invention, because neither reference teaches a method that includes delivering to any individual having otitis media and a perforated tympanic membrane, an effective, nonototoxic amount of recombinant AAT

More importantly, even if all of the claim elements were present, the combined teachings of the references would not have provided a reasonable expectation of success in practicing the invention as claimed.

The Examiner states that absent any evidence to the contrary, there would have been a reasonable expectation of successfully treating an individual having otitis media and a perforated tympanic membrane with alpha 1-antitrypsin well known by Avidano et al. having significant antiprotease activity in human otitis media sample.

Applicants traverse the rejection. First, the skilled artisan would be a person with knowledge of the treatment of otitis media in patients with a perforated tympanic membrane. Such individuals would know that there are many drugs, such as antibiotics, which may be effective in treating bacterial infections, but which absolutely cannot be used in patients with perforated tympanic membranes because such compounds are ototoxic, resulting in hearing loss. As has been noted previously, in that subset of otitis media cases presenting with perforated tympanic membrane, any compound applied topically to the external canal can readily gain access to the middle ear, and thus to the site of infection and inflammation. In these cases, however, the potential toxicity of therapeutic agents is a critical clinical concern. *See, e.g.*, Roland *et al.*, "Animal ototoxicity of topical antibiotics and the relevance to clinical treatment of human subjects," *Otolaryngol. Head Neck Surg.* 130:S57-S78 (2004) and Matz *et al.*, "Ototoxicity of ototopical antibiotic drops in humans," *Otolaryngol. Head Neck Surg.* 130:S79-S82 (2004) (already of record)

Indeed, even Avidano refers to the speculative nature of treating patients. As noted in the last paragraph of p. 350 of Avidano it is noted that "[f]urther study will be required to gain a better understanding of the various types of proteases present *and to determine the clinical utility of specific protease inhibitors* in all types of chronic otitis." Thus, the primary reference itself, calls into question the likelihood of success in using rAAT alone or in combination with other agents to treat individuals with an effective and nonototoxic amount of the agents.

To this end, Applicants remind the Examiner that the claimed invention must be considered as a whole (see MPEP 2141.02 and *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. cir. 1983)). That is, the examiner appears to have impermissibly distilled the invention to a method of treating a patient with the protease inhibitors disclosed in Avidano. However, what the Examiner has not addressed is the uncertainty and potential ototoxicity associated with actual treatment. The claims, in contrast, require the administration of an effective and nonototoxic amount of rAAT wherein there is no significant ototoxicity, elements neither taught nor suggested in the cited references.

As noted previously, prior to applicants' discovery, it could not be predicted whether AAT -- or inhibitors of matrix metalloproteases, notably ilomastat, or ilomastat in combination with AAT -- would prove sufficiently nonototoxic as to permit effective topical administration in the setting of a perforated tympanic membrane. Indeed, with agents drawn from a wide range of chemical classes having already, in some cases tragically, proven ototoxic,[1] the art instead clearly counsels caution in attempting topical therapy with novel agents. Given such caution, the cited art could not have provided a reasonable expectation that an effective, yet nonototoxic, dose of AAT or ilomastat could found that would permit successful treatment of otitis media in the setting of perforated tympanic membrane in the absence of significant ototoxicity.

Applicants submit, therefore, that the Examiner has not established a *prima facie* case of obviousness *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.").

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[1] See Roland *et al.*, Table 1.

With failure of the *prima facie* case, the burden of production has not properly been shifted to applicants, and applicants are entitled, without more, to their claims. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992).

Furthermore, Applicants respectfully submit that the ototoxicity art clearly teaches away from the use of novel compounds as topical agents, a secondary indicium of the nonobviousness of applicants' topical administration of antiprotease in the clinical context of perforated tympanic membranes.

Applicants respectfully submit that the claims as now pending would have been nonobvious over the art of record, and that the rejection is in error and should be withdrawn.

Claims 14, 20 and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Avidano et al., of record in view of Lezdey et al., as applied to claims 5, 8, 11 and 13 above and further in view of Brake et al. (U.S. Patent No 4,752,576). Brake et al., allegedly teaches a method for producing alpha 1-antitrypsin by recombinant methods from yeast.

This rejection is traversed for the following reasons.

First, only claim 14 is directed to recombinant AAT which is yeast expressed AAT. Claims 20 and 21 are not directed to yeast-expressed AAT. Brake et al. does not cure the deficiencies of the primary references Avidano et al., and Lezdey. Claims 20 and 21 are not obvious for the reasons set forth above. Withdrawal of this rejection for claims 20 and 21 is requested.

Second, claim 14 depends from claim 13. Brake et al. does not cure the deficiencies of the primary references Avidano et al., and Lezdey. Accordingly, a combination of the references does not render claim 14 obvious.

Applicants respectfully submit that the claims as now pending would have been nonobvious over the art of record, and that the rejection is in error and should be withdrawn.

CONCLUSION

Applicants submit that the present application is in condition for allowance, and respectfully request the same. If the Examiner believes that any matters remain outstanding prior to passing this case to issue, however, applicants respectfully request that the Examiner call the undersigned attorney, newly of record, for a telephonic interview.

Although no fees are believed to be due at this time, please charge any fees that might become applicable, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39042-0014**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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Date: September 14, 2006

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